Anesthesia

Introduction

This lesson is about anesthesia. The word anesthesia can refer to the specialty, the act of administering anesthetic drugs, or **insensitivity to pain**. That last one is the technical definition we are using here. It is different from analgesia—pain relief with sensation left intact. Anesthesia completely blocks the transmission of sensation.

There are three categories of anesthesia—local anesthesia, general anesthesia, and conscious sedation. **Local anesthesia** blocks the transmission of pain, either to the spinal cord or from the spinal cord to the thalamus. Local anesthesia is not sedative and doesn't involve a loss of consciousness. These act on voltage-gated sodium channels locally, not in the brain. **General anesthesia** involves a loss of consciousness. This is by far the most complex type of anesthesia, requiring multiple drugs administered simultaneously to achieve the intended effect. General anesthesia is used for long procedures (in the OR), and a subset is used in ongoing sedation for ventilation in the ICU. We'll do a deep dive in that section. **Conscious sedation** is not actually anesthesia because it does not make one insensitive to pain. Conscious sedation is a form of anesthesia (the act of administering drugs) that seeks to prevent memory formation of the event. The patient is awake and participates, but they are relaxed and won't remember the procedure. This type of anesthesia is used for minimally invasive procedures, such as endoscopy, bronchoscopy, and colonoscopy. Sedation is achieved with the "sedative and hypnotic" drug class, which we've previously discussed in regard to seizure *(Clinical Cortex #2: GABA Receptors and Alcohol)*.

We'll cover local anesthesia first (nerve blocks and spinal blocks), followed by conscious sedation (which is a review of $GABA_A$ receptor pharmacology), and then do a deep dive into general anesthesia.

Local Anesthesia

Local anesthesia is used for small procedures—inserting a needle into ascites to drain it, suturing a hand with a laceration, applying it to the oral mucosa before removing a tooth. The goal is to interrupt the pain signal, to block transmission of pain signals from ever reaching the spinal cord. The pain receptors in the skin may be firing like crazy, but if their axons are anesthetized proximal to the procedure, the action potentials that would enable the perception of pain never reach the spinal cord. Without those action potentials reaching the cortex, the patient experiences no pain.

Practically, **esters** are **reserved for topical anesthesia** of the mouth, nose, and throat. Cocaine is an ester, and it has historical significance as one of the most common subcutaneous and topical anesthetics. It also has the benefit of being a potent vasoconstrictor, which made it ideal for surgeries that involved the highly vascular nasal septum. Some ENTs still have some topical cocaine locked up somewhere. Although it is a schedule 2 drug (the same schedule as oxycodone, morphine, and dextroamphetamine), don't expect to see cocaine used as an anesthetic or have a pharmacist fill your patient's prescription. Other examples of esters include tetracaine, procaine (has the vaso-stimulatory effects like cocaine), and benzocaine. You are likely to be the most familiar with **benzocaine** as it is in over-the-counter oral anesthetics and used in the ED as "hurricane spray." If it is an ester, only use it on mucous membranes.

Amide anesthetics are separated from each other by their **time to onset** and **duration of action**, as shown below. Bupivacaine and lidocaine are commonly used for local anesthesia of the skin and are used in epidural and spinal block anesthesia (where the distribution and elimination don't matter because they are administered so closely to the spinal cord). Although any amide can be used for any purpose, bupivacaine and lidocaine are the most commonly used. You should see all the amides as equals as they can all be injected under the skin, applied to mucous membranes, or used in an epidural (spinal block). **Lidocaine** is the most popular. **Bupivacaine** is essentially a longer-lasting lidocaine.

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DRUG NAME	DISTRIBUTION (MIN) *"TIME TO ONSET"*	ELIMINATION (MIN) *"DURATION OF ACTION"*
Bupivacaine	28	210
Lidocaine	10	96
Mepivacaine	7	114
Prilocaine	5	90
Ropivacaine	N/A	N/A

Table 8.1: Amide Anesthetics and Their Differences in Distribution and Elimination

Local Anesthetic Mechanism

All local anesthetics are **injected into the skin** or applied **topically to the mucosa** near the site you wish to anesthetize. To exert its effects, the drug must diffuse from the injection site into the axon of the sensory fiber. To do that, it is going to cross multiple plasma membranes—those of astrocytes and neurons—along the way, over and over again, to reach the center of the fiber. Local anesthetics are **weak bases.** They start without a charge (lipophilic), enabling them to pass through plasma membranes. They are also able to be **protonated** and become positively charged (hydrophilic) so that they can move through the aqueous environment of the extracellular fluid or cytoplasm. This process of protonation and deprotonation continues until there is an equilibrium established between every compartment along the way.

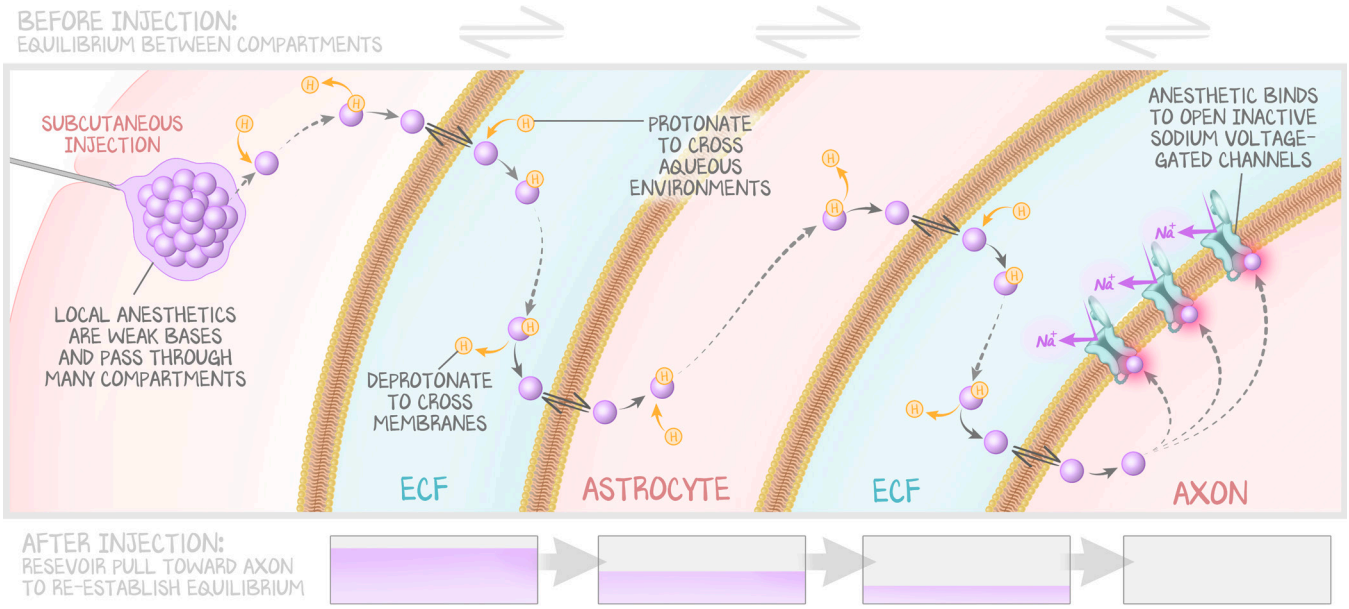

Figure 8.1: Local Anesthetics are Weak Bases
The drug is injected into the subcutaneous space. The concentration gradient favors the movement of the drug out of the subcutaneous space and into the nerve that is traveling within the subcutaneous fat. The protonated, positively charged anesthetic moves easily through aqueous environments—cytoplasm and extracellular space. The deprotonated, uncharged, nonpolar form allows diffusion through plasma membranes. As the anesthetic binds the inactivated sodium channels, it is effectively removed from the compartment that is the axon's cytoplasm. Therefore, because protonation and deprotonation are reversible reactions, and the concentration gradient favors the movement of the anesthesia deeper into the nerve (with the greatest concentration in the subcutaneous space, and the lowest concentration in the axon's cytoplasm), there will be an ever-changing equilibrium, with each compartment acting as an anesthetic reservoir. This prolongs the anesthetic effect, at least until it runs out.

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The sodium channel-blocking effects are caused by the protonated form, and only from within the cytoplasm.

The mechanism of action of local anesthetics is the **inhibition of voltage-gated sodium channels**. Action potentials are the transmission of a signal from the end of the sensory axon to the spinal cord second-order neuron. Action potentials are electrical signals, and like electricity running through a cable, the action potential in the axon decays over time and distance. In bigger axons (larger radius) or myelin-insulated axons with repeater stations (nodes of Ranvier), action potentials decay slower and persist over a greater distance.

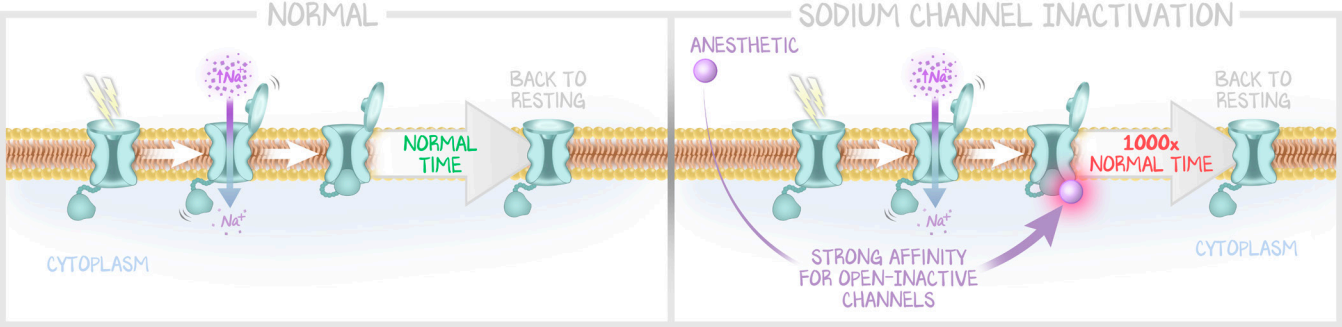

Figure 8.2: Sodium Channel Inactivation
Because local anesthetics function by blocking open (preventing Na^+ from flowing) and open-inactivated channels (preventing recovery to the resting state, General Physiology #7: *Excitable Cells Active Properties*). Anesthetic-bound Sodium Channels undergo the conformational change back to the resting state 100–1000 times slower than channels not bound by anesthetic. That means that fewer channels are ready to open, increasing the action potential threshold. And if the transmission of sensation is dependent upon how often the neuron fires (for example, sensory tracts that are reliant on the frequency of depolarizations, such as type C pain fibers), then anesthetics are more effective at inhibiting those impulses.

These are the mechanisms commonly taught—size, myelin, frequency. **Size matters—**small-diameter fibers succumb to local anesthetics more than their paired large-diameter fibers (keeping myelination constant). But **myelination matters, too—**a small, myelinated fiber will succumb to the anesthetic sooner than an unmyelinated fiber of the same size. That may not be intuitive right away—myelin is a protective sheath, and learners typically infer that means "protection against anesthetics," too. But because all the sodium channels are clustered in a tight space (nodes of Ranvier), and there is no other site to reinforce the electric signal, blocking two or three nodes terminates the entire propagation. **The frequency of depolarization matters more**. The more action potentials there are, the more often sodium channels are in their open-inactivated state, and the more the anesthetic can act to prevent future action potential propagation.

Below is an empirically derived table of fibers and anesthetic efficacy. The next paragraph will cover why.

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FIBER TYPE	TRACT	DIAMETER (μm)	MYELINATION	CONDUCTION VELOCITY (m/s)	SENSITIVITY TO ANESTHETIC
TYPE Aα	PROPRIOCEPTION, MOTOR	12–20	HEAVY	70–120	+
TYPE Aβ	TOUCH, PRESSURE	5–12	HEAVY	30–70	++
TYPE Aγ	MUSCLE SPINDLES	3–6	HEAVY	15–30	++
TYPE Aδ	PAIN, TEMPERATURE, FAST TRACT	2–5	HEAVY	5–25	+++
TYPE B	PREGANGLIONIC AUTONOMICS	<3	LIGHT	3–15	++++
TYPE C, STT	PAIN	0.4–1.2	NONE	0.5–2.3	++++
TYPE C, SYMPATHETIC	POSTGANGLIONIC	0.3–1.3	NONE	0.7–2.3	++++

Table 8.2: Nerve Fiber Properties and Anesthetic Efficacy

As it turns out, there is a surrogate for "all the features" at once—**conduction velocity matters the most**. Conduction velocity is the product of the amplitude of the action potential in the fiber, insulation by myelin, and the size of the axon. However, the frequency of firing isn't taken into account. Go back to that table of empirical evidence. Notice that as **conduction velocity increases**, **sensitivity to anesthetic decreases.** Then notice that there is a pattern to size and myelination—**decreasing size** and **less myelination** results in **increased sensitivity**. In a lab, if you take one axon of one size that is myelinated, and another axon of the same size without myelin, the unmyelinated one is more affected. Practically speaking, large, fast fibers are the least affected compared to slow, small fibers. Slow pain fibers (type C) and even fast pain fibers are affected before those of the corticospinal tracts and proprioception. Practically, the amount of anesthetic given is approximated by experience and packaging (10 mL of lidocaine comes in a paracentesis kit), and if too much is given and the entire nerve is anesthetized, the effect is only temporary.

Side Effects of Local Anesthetics

Most local anesthetics are **vasodilators**. Because the postganglionic sympathetic nerve fibers are also type C fibers, they are vulnerable to anesthetic. Losing sympathetic tone means a decrease in α_1 stimulation, a decrease in vasoconstriction and, therefore, vasodilation distal to the anesthetic. Vasodilation increases the chance that the anesthetic will enter the bloodstream and be swept away from the site of action, preventing the nerve from being anesthetized (the anesthetic reservoir also favors diffusion into the bloodstream) AND exposing the patient to systemic toxicities. For this reason, a vasoconstrictor, such as **epinephrine,** is often added to the anesthetic; most often, lidocaine and lidocaine with epinephrine are used in the hospital setting. Vasoconstriction is safe except for in the digits. The local anesthetic will work, but if administered so distally, the epinephrine may cause vasoconstriction so severe that the digits become ischemic.

If a sodium channel-blocking local anesthetic gets into the bloodstream, it can cause **cardiac arrhythmia** and **seizure.** Lidocaine was previously used for ventricular fibrillation and ventricular tachycardia. As discussed in the Cardiac module, it has been replaced by amiodarone for cardiac arrhythmias. However, lidocaine is still appropriate if amiodarone is unavailable or contraindicated, it just isn't used anymore because of the side effects. Close monitoring is required for signs of toxicity— **metallic taste, tongue numbness,** and **hearing disturbances**—because if they have those symptoms, a **seizure** will soon

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follow. You should learn that lidocaine is only used as a local anesthetic and monitor the amount used for anesthesia. The larger the total cumulative dose, the more likely it is that the patient will experience systemic side effects. **Local** anesthetics should be used **locally** and never administered intravenously.

Epidural and Spinal

The spinal cord is brain parenchyma. It has a pia mater, subarachnoid space, arachnoid, and dura. You never want to insert a needle into the spinal cord itself, but there are times that you want to get very close. Performing a lumbar puncture involves inserting a needle through the dura mater and into the subarachnoid space to sample the CSF. This is performed very low, below the cona medularis (about L4 or lower), where there is no spinal cord traveling in the CSF-filled, dura mater lined, lumbar cistern, only peripheral nerves. With anesthesia, you can perform either spinal anesthesia (enter and inject into the CSF) or epidural anesthesia (create a pocket of anesthesia just outside the dura mater).

Epidural anesthesia is usually used for surgical procedures in patients too high-risk for general anesthesia and on labor & delivery wards (for both vaginal and cesarean delivery). A needle is used to penetrate the various layers of the skin, muscles, etc., and pass through the **ligamentum flavum** of the vertebra, stopping before passing into the **dura mater.** A plastic catheter is slid into position over the needle, and the needle is withdrawn. A continuous infusion of lidocaine sustains the anesthetic reservoir. The anesthetic must be administered at a vertebral level above the level that will perceive pain. That also means that all tracts below the site will be anesthetized as well. To achieve anesthesia from labor pain, the epidural needs to be around L3 or L4, right around the vertebral level where the spinal cord tapers (conus medullaris) and forms the cauda equina. Thus, the placement of an epidural catheter at that level will enable the anesthetic to diffuse across the dura and arachnoid and catch those peripheral nerves before they reach the spinal cord. Both motor and sensory can be compromised, so the dose is adjusted until anesthesia from pain is achieved. Because mom should help the delivery by pushing, the goal is to maintain motor function and pressure sensation but eliminate pain. And because corticospinal and DCMLS nerves have the fastest conduction velocity, proper epidural anesthesia can eliminate pain without preventing mom from being unable to push with her contractions. Associate epidurals with labor and delivery.

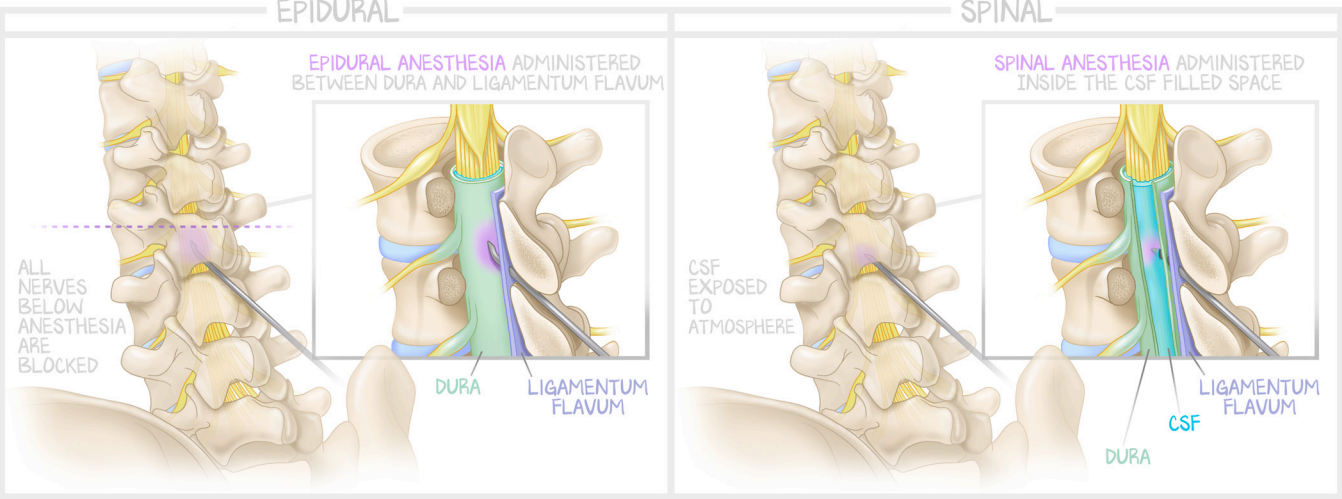

Figure 8.3: Epidural and Spinal Anesthesia
Epidural anesthesia does not enter the CSF-filled subdural space and poses little risk for traumatizing the cord. It can be performed at any vertebral level but will also risk anesthetizing the tracts from vertebral levels below. Spinal anesthesia enters the CSF-filled space, so it should not be attempted above the conus medularis, i.e., above L3.

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Spinal anesthesia involves starting the catheter in the CSF. The differences between spinal and epidural anesthesia are that **much less anesthetic** is needed for a spinal and a spinal catheter exposes the CSF to the atmosphere. Spinals are usually "once in, inject and withdraw." Epidurals can be infused and titrated to effect. If too much anesthetic is administered, the patient may experience **frank hypotension** due to the loss of sympathetic tone because the spinal cord reaches L3 in 2% of adults and L4 in such a low number that it is difficult to report. Thus, the L3–L4 or L4–L5 intervertebral space should be chosen. Associate spinal anesthesia with genital, urinary, and lower body procedures.

Conscious Sedation

The most common modality of conscious sedation is the use of the benzodiazepine **midazolam**. It has the fastest onset and recovery times. That is, the patient is pre-medicated with an intravenous dose, the procedure is performed, and then the patient wakes up in the recovery room and goes home. This is great for outpatient procedures that are invasive but do not require general anesthesia, so associate conscious sedation with scopes—endoscopy, colonoscopy, bronchoscopy. We've already talked a lot about $GABA_A$ receptors, so we won't belabor the point. $GABA_A$ receptors increase conductance to chloride when activated by GABA, hyperpolarizing postsynaptic centers and inducing amnesia, myorelaxation, and cerebellar ataxia. The amnesia and cerebellar ataxia are why patients shouldn't be allowed to drive themselves home. Patients who are given benzos are effectively severely inebriated—disinhibited, uncoordinated, and amnesic—similarly to those under the influence of alcohol.

Another form of conscious sedation that is often used in children is the drug **ketamine**. Ketamine is an **NMDA antagonist.** Therefore, it targets a glutamate (a physiological GABA antagonist) receptor. It has no effects on AMPA and is selective for NMDA. The outcome of NMDA receptor antagonism isn't easily deduced, and it is very different from that of $GABA_A$ receptor activation. Ketamine creates a **dissociative state**, in which the patient is conscious and aware; it is as if the patient's consciousness is out of body, the pain happening to someone else**.** It also provides **intense analgesia**. Its use as an anesthetic is often limited to short procedures in **young patients** that require **intense analgesia**. It can also be used in times of hemodynamic compromise, as its common side effects—**tachycardia and hypertension—**are desired, whereas every anesthetic discussed thus far will likely exacerbate hypotension. Ketamine is also a drug of abuse, called Special K (and not the cereal) amongst other street names.

Propofol and **etomidate** can be used for conscious sedation and as induction agents. We want to keep things organized in very clear, discrete, nonoverlapping uses. So, we want you to learn propofol and etomidate are used in general anesthesia only

General Anesthesia

Generalized anesthesia must accomplish five goals—**amnesia**, **analgesia**, s**keletal muscle relaxation, inhibition of autonomic reflexes,** and **unconsciousness**. We are going to teach this practically as we move through the next few sections. But before we begin, we want you to link amnesia with $GABA_A$ receptor, analgesia with μ receptor, and skeletal muscle relaxation and the inhibition of autonomic reflexes with nicotinic acetylcholine receptor (nAChR). Loss of consciousness comes with a combination of these drugs. No one agent does them all, so **balanced anesthesia** (a combination of drugs without overlapping mechanisms used in concert) requires multiple drugs to achieve all five goals.

Practically speaking, we're going to approach this as if we were in the OR, about to perform a long procedure. There are things that can be done prior to arrival in the OR, then three phases—induction, intubation, and maintenance. Most include intubation with induction, but by breaking it out, we can link a medication class to a phase of general anesthesia and further link separate anesthesia goals to that drug class. Again, this is an oversimplification, but the discrete columns of the following figure will help you keep things straight. This figure serves as a preview of the sections to follow.

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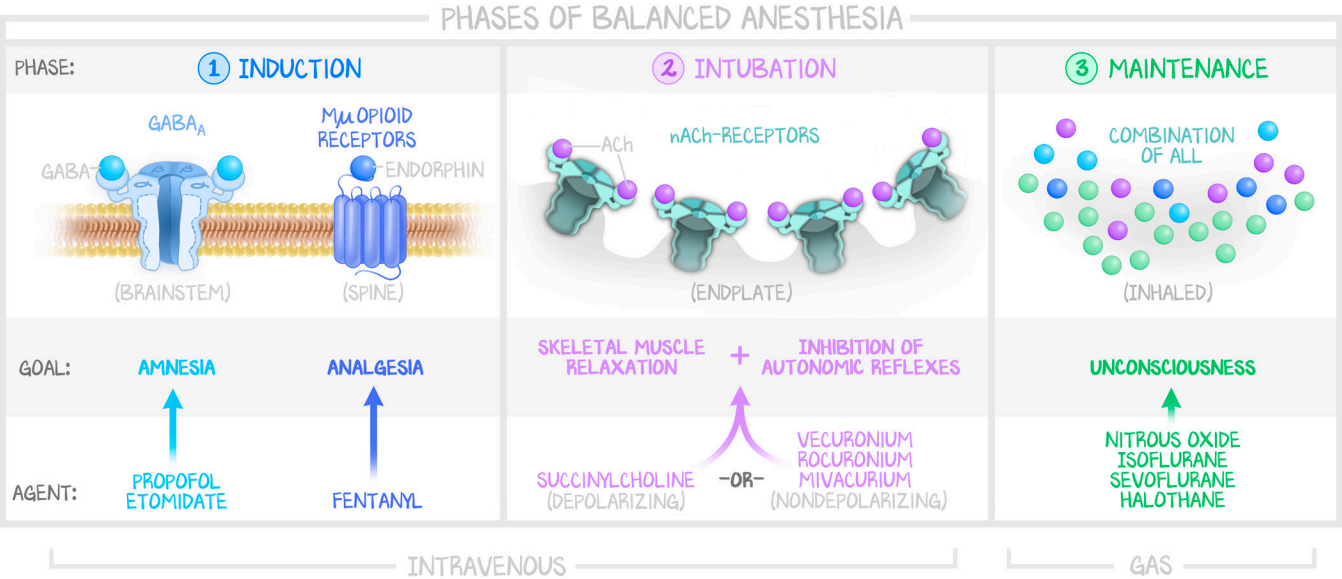

Figure 8.4: Phases of General Anesthesia
This is the preview and the takeaway—three phases, each with their associated receptors and intended effects. Induction occurs in the operating room. Induction achieves amnesia (via activation of $GABA_A$, achieved with propofol or etomidate) and analgesia (via activation of μ opioid receptors (MOR), achieved with an opioid) to prepare the patient for intubation. Intubation, securing a patent airway for the procedure, is accomplished by paralyzing the patient, thereby maximizing visualization of the larynx and passage of the endotracheal tube. Succinylcholine is a rapid on and short duration medication (best used in airway emergencies and status epilepticus in order to monitor seizure contractions) and is also a depolarizing agent (avoid in hyperkalemia). The -curoniums are nondepolarizing. Induction drugs are administered first as the paralytics do not confer analgesia or amnesia. Maintenance is achieved with inhaled gases that, contrary to what we said earlier, somehow manage to achieve all of the desired effects of balanced anesthesia. Practically, intravenous medications make things go faster and easier, and once the patient is on the operating table, intubated, and draped, then switching to the inhaled anesthetic enables the patient to be rapidly situated. Although the other drugs wear off, the inhaled anesthetic maintains the patient for the duration.

Induction

Induction does two things—stimulates analgesia (MOR activation) and stimulates amnesia with impaired awareness ($GABA_A$ receptor activation). Because we are discussing the operating room process, intravenous access is assumed. Again, for induction, we want rapid-acting agents.

For **analgesia**, opioids are used. The most common is **fentanyl**.

For **amnesia and awareness**, a few different agents could be used. Benzodiazepines**,** usually in the form of rapid-acting midazolam, can be given before transport to the OR, prior to induction. However, they are rarely chosen as the induction agent for surgery. **Rapid-acting barbiturates,** such as thiopental and methohexital, have essentially been replaced by newer, more titratable, more predictable agents, such as **propofol** and **etomidate**.

Propofol is the first-line agent and the most used induction agent for non-emergent surgery (where comorbidities and hemodynamics determine the selection, which is way out of scope for this lesson). Propofol activates $GABA_A$ receptors, achieving the necessary sedation and amnesia. It has no analgesic properties and is commonly used in combination with fentanyl. It has the **largest impact on blood pressure,** causing **hypotension**. Long-term use can result in propofol infusion syndrome, a catastrophic, insidious-onset version of malignant hyperthermia (discussed below) that presents with rhabdomyolysis, renal failure, and cardiorespiratory arrest. Prolonged propofol infusion is usually seen in the intensive care unit and not in the OR, where a single injection of propofol is administered.

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Etomidate is the "other propofol," chosen for the same indications but used in patients who can't tolerate blood pressure swings. It is also chosen in emergent situations, such as rapid sequence intubation, because of its limited effects on blood pressure. Like propofol, it acts on $GABA_A$ receptors, inducing amnesia but not analgesia.

See propofol as the bolus drug in the OR, etomidate as the bolus drug in the ER, and propofol infusion as the infused drug in the ICU.

Intubation = Paralytics

Thee paralytic agents are used to **facilitate intubation**, prevent unexpected movement or the autonomics from doing something funky (both are 'motor'), and ensure immobility. Not all pain reflexes are mitigated by the cortex. And although anesthesia makes the patient unaware of what's happening, the spinal cord and brainstem reflexes may still cause problems for the operating surgeon. This is especially true in the acute setting, where a patient may not be optimized for intubation (e.g., they are acutely ill) but needs it. Induction takes care of the cortex, and paralytics take care of the skeletal muscle.

There are two types of neuromuscular junction (NMJ) blockers: depolarizing and nondepolarizing. Succinylcholine is the only depolarizing NMJ blocker that we want you to learn. It shares no similarity to the other nondepolarizing NMJ blockers beyond their indication—induce paralysis. Keep them separate. Succinylcholine depolarizes, -curoniums don't.

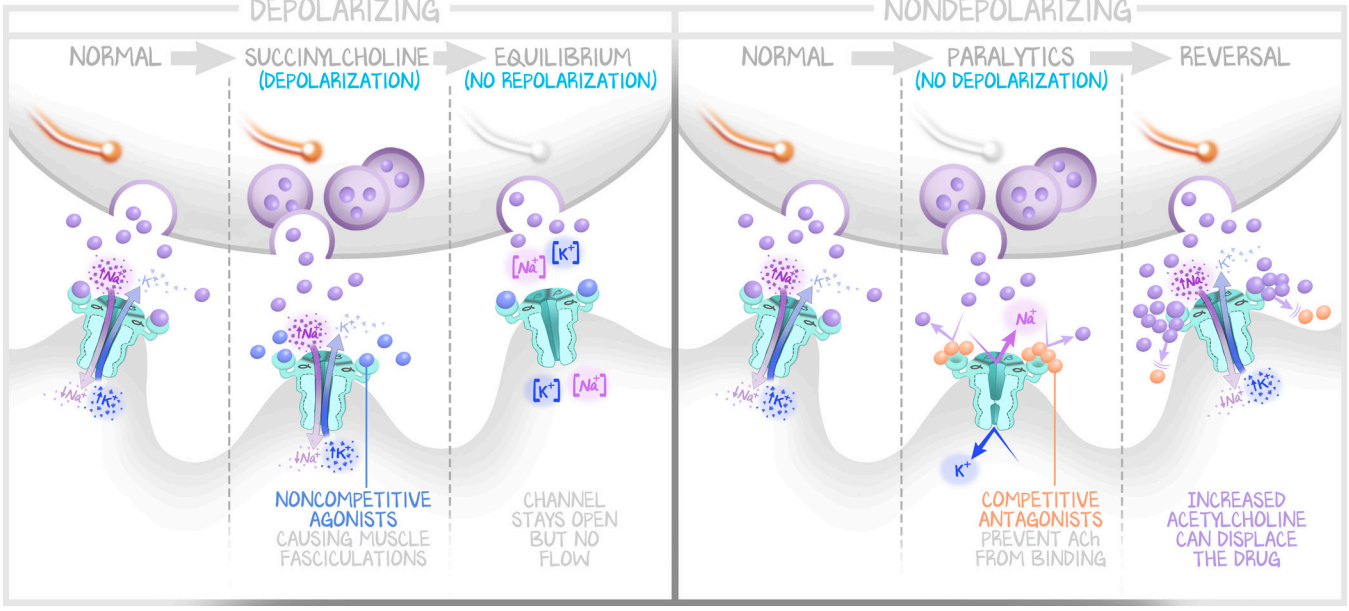

Figure 8.5: Paralytics
Succinylcholine causes paralysis in two phases. The first is depolarizing, inducing fasciculations and preventing repolarization. The second phase is desensitization. Even though the endplate does eventually hyperpolarize, the succinylcholine remains bound to the acetylcholine binding site, thus preventing endogenous acetylcholine from binding, and keeps the channels open. Nondepolarizing agents prevent endogenous acetylcholine from binding its receptor (competitive antagonism), but they don't activate the receptor.

Succinylcholine is a **depolarizing** NMJ blocker that causes the depolarization and contraction of skeletal muscles, as evidenced by fasciculations after administration. Succinylcholine binds to and activates the nACh receptors in skeletal muscle. The affinity of succinylcholine for the receptor is strong, so it binds tightly, depolarizing the skeletal muscle, and doesn't let go. Succinylcholine remains

bound, keeping the channels open and preventing repolarization, which is required for voltage-gated sodium channels to close their inactivation gates. Without repolarization, excitable cells cannot conduct another action potential. Succinylcholine has a rapid onset (30 seconds) and a short duration of action (approximately 6 minutes) because of its degradation by endogenous cholinesterases. Because the binding affinity is so high, adding an acetylcholinesterase inhibitor, which would cause the accumulation of acetylcholine in the synaptic cleft, would not reverse succinylcholine.

Nondepolarizing NMJs all contain "curonium" in the body of their name and end in "-ium." Examples include vecuronium (colloquially "Veck"), rocuronium (colloquially "Rock"), and mivacurium (doesn't follow the -curonium rule but also not used often). These are **competitive ACh receptor antagonists.** They have a higher affinity for the acetylcholine receptor than that of acetylcholine but do not induce depolarizing stimuli. Because they are competitive, increased acetylcholine can displace the drug and activate the skeletal muscle. Thus, reversal can be achieved with **acetylcholinesterase inhibitors,** such as neostigmine, or the administration of quaternary acetylcholine analogs, such as glycopyrrolate. Because these do not depolarize the skeletal muscle, there is no risk of hyperkalemia; thus, these are safe to use when the potassium level is already elevated.

Maintenance = Inhaled Anesthetics

Inhaled anesthetics have a poorly elucidated mechanism of action, but they seem to be NMDA (glutamate) antagonists, $GABA_A$ receptor agonists, and nACh receptor antagonists. Although not mediated through **μ** receptors, they also block spinal transmission of pain. Basically, they do everything a general anesthetic should. They don't paralyze as well or as quickly as the paralytics. They don't induce amnesia or analgesia as well as the direct-acting medications. But they can maintain the effects already stimulated by other agents. This is why induction and intubation start with the administration of direct-acting intravenous agents, and the patient is switched to inhaled anesthetic as the surgery progresses. Along the way, other intravenous agents can be administered as needed.

In the United States, nitrous oxide is typically used for in-office procedures, and **isoflurane** and **sevoflurane** are used in the operating room. On licensing exams, you will see **halothane**, which isn't used anymore because of its **hepatotoxicity** and high risk of **malignant hyperthermia** (below).

How these drugs interact with distribution and potency comes up on licensing exams. And MAC, but we encourage you to ignore MAC for reasons we are about to explain.

Distribution is about the speed of onset and speed of wearing off. It has to do with the **solubility of a gas in the blood**. Inhaled anesthetics are delivered to the alveoli. The partial pressure of the gas favors its diffusion into blood, just like that of oxygen. For the gas to leave the bloodstream, it must "get out of the blood." The more soluble it is in blood, the more the gas likes being in blood, and the longer it takes for it to get out of the blood in order to become a gas again and exert its effects. You want the gas in the patient's CNS, not in their blood. Therefore, the **lower the solubility in blood**, the **faster the onset will be**. This is communicated by the **blood-gas solubility coefficient**. The lower the number, the faster the onset, and the faster the recovery will be.

Potency is physiologically determined by the **oil-gas partition coefficient**. The gas has to pass through lipophilic plasma membranes in order to access the CNS. Potency determines the relative dosing required to achieve an effect. It has been measured empirically. The **more lipid-soluble the gas is, the greater its potency** (i.e., a lower dose is required to achieve the effect). Lipid-soluble and oil-gas partition coefficient are the same thing. But, of course, medical science couldn't stop there—lower solubility in the blood means faster onset, higher lipid-solubility means a lower dose is required. Instead, they came up with the MAC. And not monitored anesthesia care, but the **minimum alveolar concentration**. Not blood, not lipid, not coefficient, but alveolar concentration. And what is the MAC? The **inverse of lipid solubility**.

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WHY!? Why take a 2×2 grid that is a perfect opposite and introduce an inverse to one of those things on the grid? It can only serve to muddle and confuse. Which of the two is it the inverse of? The introduction of MAC, in regard to teaching this subject, increases the possibilities from four permutations to eight. MAC is clinically useful because it informs the person who is giving gas to a human and needs to be able to decide how much gas to give. The anesthesiologist doesn't measure lipid solubility or blood solubility. It's just frustrating because MAC is already represented by lipid solubility. The higher the air-lipid solubility, the great the potency, and therefore the less gas you need to achieve the intended effect. In short, the better a drug works, the less you need to give. Oh wait, I meant gas, not drug. Wait. Oh, they are the same thing, expressed in different words that mean the same thing.

The max dose of captopril is 150 mg per day. The max dose of lisinopril is 40 mg. Both are ACE-inhibitors. Captopril is taken three times a day because it has a short half-life, whereas lisinopril is taken once a day. The milligram values differ, and the frequencies differ. If they were gases, we would say captopril has a low blood-gas partition coefficient (requires three doses per day so is faster on and faster off), a lower oil-gas partition coefficient (needs more milligrams to achieve the effect), and therefore a higher MAC (150 mg is greater than 40 mg).

Malignant Hyperthermia

Malignant hyperthermia is a life-threatening reaction to inhaled anesthetics. It is caused by an **autosomal dominant** mutation of the skeletal muscle **ryanodine receptor**. We discussed the details of this receptor in General Physiology #12: *Skeletal Muscle.* An action potential travels from the motor endplate and along the plasma membrane of the skeletal muscle. Invaginations of the plasma membrane are flanked by sarcoplasmic reticula, forming the T-tubule. Voltage-gated calcium channels are in the plasma membrane, connected to the ryanodine receptor. When the voltage-gated channel opens in response to the action potential, it allows a small amount of extracellular calcium into the cytoplasm, but its main effect is to **open ryanodine receptors**. The conformational change in the voltage-gated calcium channels causes the lid that blocks the flow of calcium through the ryanodine receptor to become displaced. Calcium floods the cytoplasm, stimulating muscle contraction. Under normal conditions, unless there are more depolarizations of the endplate, the voltage-gated calcium channels switch back to their resting form and close the lid of the ryanodine receptors. Contraction ends.

In patients with the mutation, the **ryanodine receptor stays open** when they are exposed to an inhaled anesthetic. As long as the gas is present, an extraordinary amount of calcium remains in the cytoplasm. This happens in every skeletal muscle cell everywhere. All skeletal muscles contract with maximal force, **massively increasing metabolic demand** to well beyond what the skeletal muscle glycogen stores and the delivery of oxygen and glucose can sustain. Malignant hyperthermia can even occur despite paralysis, as paralytics block the receptors at the endplate, whereas the gas affects the sarcoplasmic reticulum (although the effects are mitigated by the paralytic). Most importantly, malignant hyperthermia happens early, at the start of the inhaled anesthesia. If it doesn't happen, it won't later.

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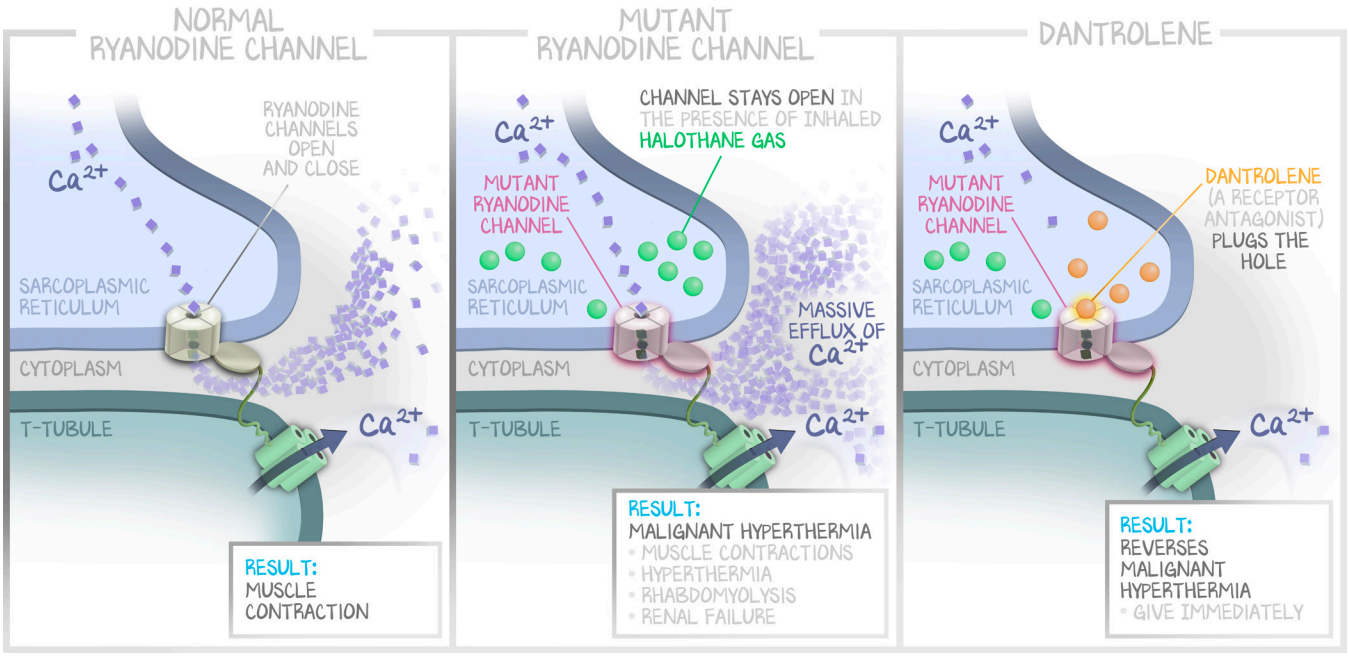

Figure 8.6: Malignant Hyperthermia
A normal ryanodine channel (receptor and channel are used interchangeably in the literature) opens due to an action potential on the plasma membrane. It is opened by the conformational change of voltage-gated calcium channels, removing the lid to reveal a calcium channel with high conductance. In patients with mutant receptors, the ryanodine channels don't close, and a massive calcium efflux into the cytoplasm results in sustained contraction of maximum force. The gas is turned off, and dantrolene is administered. Dantrolene plugs the ryanodine channels, allowing for the calcium to be pumped back into the sarcoplasmic reticulum and entirely preventing calcium efflux.

All the muscle contraction and ATP production generates heat, so much so that the patient experiences **hyperthermia**. This is not a fever but rather elevated temperature due to work being done. If not intervened on, skeletal muscle cells will die. Before they do, they release myoglobin into the bloodstream—**rhabdomyolysis.** Myoglobinemia results in myoglobinuria, which can lead to renal failure. If malignant hyperthermia occurs, immediate discontinuation of the gas and intravenous administration of **dantrolene**, a ryanodine receptor antagonist that plugs the pore, thus preventing any calcium from leaving the sarcoplasmic reticulum and enabling the endogenous channels to pump the calcium back into the sarcoplasmic reticulum, aborting the pathology.

Common Practice Combination Uses

Rapid-Sequence Intubation. Etomidate and vecuronium (or succinylcholine). Etomidate induces amnesia and loss of consciousness. The paralytic paralyzes the patient. The tube is placed. The tube is connected to a ventilator, and an infusion of propofol and fentanyl are started as maintenance. Both are stopped daily to assess if the patient can come off of those infusions or off of the ventilator. Etomidate and vecuronium are used in **induction**. Propofol and fentanyl are used in **maintenance**.

Prolonged Surgery. A preoperative benzodiazepine is sometimes given, but not always. The benzo is usually the very fast-acting midazolam (**pre-induction**). In the OR, they are given intravenous fentanyl (μ receptor agonist, analgesia) and intravenous propofol ($GABA_A$ receptor, amnesia). When the patient is adequately sedated, vecuronium (or succinylcholine) paralyzes the patient. They are intubated (**induction**). The surgery begins, and an inhaled anesthetic (usually isoflurane or sevoflurane) is administered for the duration of the procedure (**maintenance**).

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